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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,124	07/25/2003	Maria Tang	10302.200-US	4207

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NOVOZYMES, INC.
1445 DREW AVE
DAVIS, CA 95616

EXAMINER	
GRASER, JENNIFER E	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,124	TANG ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9,12,15,20-23,28,31,34,39-42,47 and 50-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,12,15,20-23,28,31,34,39-42,47 and 50-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/25/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/4/06 has been entered.

Acknowledgment and entry of the Amendment submitted on 12/4/06 is made. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50-73 are currently pending. It is noted that claims 58-73 are listed as being 'new claims'. It is noted that these claims are not newly presented claims. They were submitted on 12/2/05. Their status should be updated.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because is unclear whether the first and second nucleic acid sequences are a fusion/hybrid sequence. Is this mutant cell transformed with the first and second nucleic acids? What type of mutation is encompassed by the

claim? The specification appears to recite full-length gene deletions only; however, the instant claims appear to read on any insertion, substitution, partial deletion, etc.. Clarification is requested.

Claims 15, 34 and 70 are vague and indefinite because they require that the mutant cell produce at least about 25% less of the red pigment compared to the parent Bacillus cell when cultured under identical conditions. It is unclear what type of mutations would render a cell with this phenotype. What type of mutation would render this phenotype. The location/type of mutation is a critical limitation. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claims 60, 65, and 71 are vague and indefinite due to the phrase "comprises a mutation of one or more genes which encode a protease". The claim fails to teach what type of mutation or what phenotype is rendered by the mutation. Additionally, the claims encompass any species of Bacillus and it is unclear what genes are encompassed by the term 'protease'. The mere recitation of a name, i.e., protease, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. Further, the name "protease" is used for many other proteins/protein fragments in the art. The claim should provide any structural properties, such as the amino acid sequence of the protein or nucleic acid

sequence of the gene, which would allow for one to identify the 'protease' without ambiguity. The mere recitation of a name does not adequately define the claimed protein.

Claims 60, 61, 62, 66, 72 and 73 are vague and indefinite. Claim 62, 67, 72 and 73 recite a 'mutant cell [which] further comprises a modification of one or more genes selected from the group consisting of spoIIAC, srfA, srfB, srfC,, srfD, and amyE". It is unclear what is encompassed by the term 'modification'. How are these genes 'modified'? What phenotype does the modification/mutation produce? Additionally, the mere recitation of a name, i.e., spoIIAC, srfA, srfB, srfC,, srfD, amyE, nprE, aprE, etc., to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claims encompass any species of Bacillus and it is unclear what structure is encompassed by these names. Further, the names are used for many other genes/proteins in the art. The claim should provide any structural properties, such as the amino acid sequence of the protein or nucleic acid sequence of the gene, which would allow for one to identify the ''genes' without ambiguity. The mere recitation of a name does not adequately define the claimed genes. The type of mutation and the phenotype it produces should also be recited in the claim.

Claim Rejections - 35 USC § 112-Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "A method of producing a heterologous protein, comprising: transforming a mutant *B.subtilis* cell, wherein said mutant cell comprises a deletion mutation in the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said deletion mutation renders the cell deficient in red pigment compared to a wild-type *B.subtilis* cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, with a recombinant vector comprising a nucleic acid directing synthesis of the heterologous protein and recovering the heterologous protein from the cell"; "a mutant *B.subtilis* cell, wherein said mutant cell comprises a deletion mutation in the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said deletion mutation renders the cell deficient in red pigment compared to a wild-type cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, and a recombinant vector comprising a nucleic acid directing synthesis of a heterologous protein"; and "A method of obtaining a mutant *B.subtilis* cell, comprising: making a deletion mutation to the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said mutation renders the cell deficient in red pigment compared to a wild-type *B.subtilis* cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7", does not reasonably provide enablement for the scope of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant has also not provided sufficient information for one of skill in the art to make or use the claimed polynucleotides without undue experimentation. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, such that one skilled in the relevant art could make or use the invention without undue experimentation, the courts have put forth a series of factors that may be considered. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). These factors include the following: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The claims are drawn to a method of producing a heterologous protein which uses a mutant Bacillus bacterium wherein the mutant is obtained by mutating *any* cypX or yvmC gene from *any* bacterium of the Bacillus Genus wherein the nucleic acid is at least 70% identical to the cypX and yvmC nucleic acid sequences of SEQ ID NO: 1 and 7, respectively. The claims also are drawn to the mutant bacterium cells and methods of isolating the mutant bacterium cells.

The instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification is only enabled for methods which use *B.subtilis* genes and mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and not the broad scope of the claims. It would take one of skill in the art undue experimentation to discover new red pigment genes in any of the other 14 species of *Bacillus*, much less the more than **208** species of Bacillus known and classified in the prior art. Bacterial species often times do not produce the same proteins. The prior art is silent as to whether any other species of Bacillus possess the *cypX* and *yvmC* proteins and, therefore, it would take one of skill in the art undue experimentation in order to isolate the claimed DNA sequences from any species of bacteria other than *B.subtilis*. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague

intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

In the present case, the applicant has neither provided any direction or.guidance, nor any working examples in the specification as to any potential mutations of SEQ ID NO: 166 that would satisfy the limitations of the claims. However, the claims read on any mutation to that sequence, and to homologs thereof, that have the effect of decreasing the activity of the gene product. Just as the breadth of the claims is great, so is the number of potential mutations that may be made. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue experimentation.

While those participating in the art of the relevant technology (genetic and protein manipulation) are generally highly skilled, the art is also rife with complexity. See also,

discussion below in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the sequence of protein of polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, supra. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are.

The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the cypX or yvmC coding region to target for modifications, in order to produce a bacterium which produces at least 25% less red pigment than the parent cell. Applicant's demonstration in the instant does not enable one skilled in the art to make mutations in any Bacillus bacterium, in such a way as to not only attenuate the bacterium through the specific mutation of the cypX or yvmC coding sequence, but to also decrease the cypX or yvmC biological activity in such a way that it is responsible for the resultant bacterial phenotype.

First, one would have to first discover another species of Bacillus with an cypX or yvmC gene which is at least 70% identical to SEQ ID NO:1 or 7. Then, one would have to produce specific mutations and test for function. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." General guidance does not provide specific guidance for what mutations in the yvmC or cypX scoding sequence that would result in the desired cell lines. Bowie et al is cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

Claims 60, 61, 62, 66, 72 and 73 recite mutant Bacillus cells with one or more additional modifications to 8 different genes, e.g., spoIIAC, srfA, srfB, srfC,, srfD, and amyE, nprE and/or aprE and any mutation of any gene encoding any protease, also from any species of Bacillus. Short of the description on page 18 and pages 22-23 which disclose *Bacillus subtilis* strain RB128 is a Bacillus subtilis A164A5 strain (Bacillus subtilis ATCC 6051A deleted at the spoIIAC, aprE, nprE, amyE, and srfC genes), the specification provides no other description of other species of Bacillus with deletions to these same genes. Additionally, the specification fails to teach how these genes were mutated. Were these deletions full-length deletions, partial deletions, etc.? It is unclear that each of these genes is present in all species of Bacillus and were well known in the prior art at the time the invention was made. It would take undue experimentation for one of skill in the art to *discover* these genes in other species of Bacillus and make appropriate gene 'modifications' because it is unclear what type of modification is encompassed. The specification is silent as to the embodiments of this language.

Claims 15, 34 and 70 require that the mutant cell produce at least about 25% less of the red pigment compared to the parent Bacillus cell when cultured under identical conditions. It is unclear what type of mutations would render a cell with this phenotype. The specification fails to teach or suggest a specific mutation which would render a cell with this phenotype.

Response to Applicants' Arguments:

6. Applicants argue that it would not take undue experimentation to practice the claimed invention. They state that a certain amount of routine experimentation is permissible. They argue that they are enabled for the broad scope of the invention because they have shown in Example 6 that primers based on the *cypx* gene from *B.subtilis* were used to clone by PCR the *cypx* gene from *B.licheniformis* and delete a portion to prevent formation of the red pigment. They further argue that they describe methods for isolating *cypX-yvmC* operons from *B.subtilis* and *B.licheniformis*. They argue that it is within the skill of the art to "discover new red pigment genes in other species of *Bacillus* using Applicants' disclosure. These arguments have been fully and carefully considered but are not deemed persuasive in overcoming the rejection.

The instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in the instant claims, or the more than **208** species of Bacillus currently known and categorized, possess *yvmC* and/or *cypX* genes. At the very least, the specification has only shown that *B.licheniformis* possesses a *cypx* gene which can produce red

pigment. The prior art is silent as to whether any other species of Bacillus possess the *cypX* and *yvmC* proteins and, therefore, it would take one of skill in the art undue experimentation in order to isolate the claimed DNA sequences from any species of bacteria other than *B.subtilis*. The specification only enables deleting or mutating the *cypX* and *yvmC* from B.subtilis and the *cypX* gene from *B.licheniformis* in order to get better expression of a heterologous protein. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Claim Rejections - 35 USC § 112-Written Description

7. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a mutated Bacillus bacterium (or use of said bacterium) which is obtained mutating *any* cypX or yvmC gene from *any* bacterium of the Bacillus Genus wherein the gene is at least 70% identical to the cypX or yvmC nucleic acid sequences of SEQ ID NO:1 or 7. Mutant Bacillus bacterium comprising any modification/mutation to a gene encoding any protease and modifications/mutations to one or more of spoIIAC, srfA, srfB, srfC,, srfD, amyE, nprE, aprE are also claimed. However, the specification does not provide adequate written description to support either species homologs to SEQ ID NO: 1 or 7, or any mutation resulting in the specific phenotype.

There is inadequate written description to support claims to species homologues of the disclosed polynucleotide.

The instant specification has only taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species

of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification only provides adequate written description for methods which use *B.subtilis* genes and mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and not the broad scope of the claims.

The applicant has not identified any common structural core which one skilled in the art could use to identify any genus of polynucleotides. In essence, the applicant is claiming such polynucleotide homologues only by their functionality, that of encoding producing red pigment. More than a statement of biological function is required to satisfy the 112 1st paragraph written description requirement for a genus of DNA molecules. See e.g. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chugai, the Court of Appeals for the Federal Circuit stated that "[i]t is not sufficient to define [a DNA] solely by its principal biological property, e.g. encoding of human erythropoietin." Id., at 1021. Rather, "what is necessary is that [the applicant] provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id., at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 ¶1 written description requirement.

More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated

that defining a cDNA by its function "is only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus [of claimed cDNAs] that distinguish them from others." Id. Thus, it is clear that identification of polynucleotide by naming the polypeptide it encodes is not sufficient. In the present case, the only description that the applicant has provided for species homologues of SEQ ID NO: 1 and 7 is that they must also encode red pigment proteins. Such a description is clearly insufficient to support the claimed genus. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the yvmC or cypX coding regions to target for modifications, in order to produce the desired bacterium,e.g., produces 25% less red pigment. While it may be obvious to those in the art to make mutations in a gene or protein, to achieve an mutated bacterium, once the molecule has been identified as necessary for the specific phenotype of the bacterium, it is not immediately obvious to those in the art as to what mutations will be effective. See e.g., Bowie et al., Science 247:1306-1310, page 1306. Bowie et al. presents a discussion on the tolerance of proteins to substitutions in the residue sequence. Although the reference is a discussion of protein substitutions, as the present case is concerned with polynucleotides encoding such proteins, the teachings of the reference are equally applicable to the mutations of the claimed inventions. The reference states first that proteins generally accept a wide variety of substitutions in their residue sequence. However, it also states that some residues may not be substituted at all without loss of the proteins function. The reference also states that the

effects of such substitutions are, currently, highly unpredictable.Thus, one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutation (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity.

As stated above, the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description and enablement requirements. In the present case, not only does the application claim additional undisclosed polynucleotides without such support, it further claims modifications to both the disclosed and undisclosed polynucleotides by the effect of such modifications.

Applicants are claiming bacteria and they are claiming said bacteria comprising a mutation in a nucleotide sequence with a specific structure: function relationship in the claims. "The Applicant's are not claiming polynucleotide sequences per se."

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the coding sequence of the cypX and yvmC polynucleotide sequences recited in the claims, but the polynucleotide sequence must additionally be mutated in such a way as to decrease the cypX and yvmC biological activity in order to reduce the amount of red pigment produced by the bacteria. The polynucleotide sequence, as well as the specific mutation(s) of the polynucleotide sequence to accomplish decreased biological activity of the encoded polypeptide, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:1 and 7, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and mutant cells. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The product itself is required.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of other species of bacteria and potential genes encoding red pigment proteins is made. This is insufficient to provide Written Description to support the generic claims.

Response to Applicants' Arguments:

8. It is the position of the examiner that Applicant has disclosed polynucleotide coding sequences for cypX SEQ ID NO 1 which encodes for SEQ ID NO 2 (amino acid sequence) and yvmC SEQ ID NO 7 (encodes SEQ ID NO 8), but claims mutant strains of bacteria from any member of the bacterial family of Bacillus, which includes and is not limited to more than **208** species of bacteria, which include many more strains, species, and serotypes of these bacteria. In the instant claims, with the exception of SEQ ID NO:1 and 7, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

The Specification does not provide any examples or provide any detailed description of the cypX or yvmC, spoIIAC, srfA, srfB, srfC,, srfD, and amyE, nprE and/or aprE genes such that one skilled in the art would be aware of, or recognize that

Applicant was in possession of, any such mutated bacterium from other species of Bacillus. Applicant has not provided any guidance as to which parts of the gene are susceptible to mutation such that they would result in the expression of an inactive or less active protein thereby resulting in decreased red pigment and attenuation of the bacterium. There is no description of any of the gene mutations, or any targets for mutation, that could yield the intended results. The specification and claims fail to teach or suggest what is the desired phenotype of the numerous mutations to any protease, or spoIIAC, srfA, srfB, srfC,, srfD, and amyE genes.Thus, the applicant has not provided any working examples of or any guidance towards, the claimed mutations. The applicant is therefore claiming, as indicated in the prior action, a genus of mutated bacteria solely by their intended effects, without providing any structural or other information by which one skilled in the art could identify the claimed inventions.

Applicants argued that there is no need for a detailed description of every cypX or yvmC gene because it is only the phenotype of the bacterial strain by mutation that produces the desired result that is important and one of skill in the art could screen for mutants strains within the claimed genus. While the Examiner agrees with certain individual statements made by the Applicant, the Examiner respectfully disagrees with the argument as a whole. The Examiner agrees that the application need not describe every possible change to the coding sequence for a polypeptide that would result in meeting the claims' functional limitations. However, such does not absolve the Applicant of the need to provide some structural description by which those in the art could distinguish mutated genes resulting in the attenuated bacterium. Applicant must

describe a representative number of species for a claimed genus, but what is now claimed, is a highly variable genus (mutant poly-nucleotides) which result in variable levels of biological activity, and expression (see all claims), for which the two disclosed species are not representative. Further, the present claims do not read on attenuated bacterial cell mutated by any means, but require a mutation in a specific genetic coding sequence- the cypX or yvmC, spoIIAC, srfA, srfB, srfC,, srfD, and amyE, nprE and/or aprE polynucleotide coding sequences. Thus because the present claims are so limited, the applicant is required to provide some structural description surrounding the claimed functions. In the present case, this means that the Applicant must provide sufficient descriptive support such that one skilled in the art could determine to some degree, other than by testing function, whether a bacterium with a particular mutation in the cypX or yvmC, spoIIAC, srfA, srfB, srfC,, srfD, and amyE, nprE and/or aprE polynucleotides would fall within the claims. As the applicant has not provided any means by which such a person could distinguish fully operative mutants from those which lead to attenuated phenotypes, the Applicant has not provided adequate written description for the claimed invention.

Applicants argue that one of skill in the art would be able to discover cypX or yvmC, spoIIAC, srfA, srfB, srfC,, srfD, and amyE, nprE and/or aprE genes from the other 208 or more members of the Bacillus bacteria and mutate these genes in a manner to obtain the desired bacterium. They argue one would not need to know the complete sequence of an yvmC or cypX homolog to make and/or use the invention.

The specification has only provided examples with 2 of the 208 or more species of the Bacillus members.

As stated above, the application need not describe every possible change to the coding sequence for a polypeptide that would result in meeting the claims' functional limitations. However, such does not absolve the Applicant of the need to provide some structural description by which those in the art could distinguish mutated genes resulting in the attenuated bacterium. Applicant must describe a representative number of species for a claimed genus, but what is now claimed, is a highly variable genus (mutant poly-nucleotides) which result in variable levels of biological activity, and expression (see all claims), for which the two disclosed species are not representative. Further, the present claims do not read on a bacterial cell mutated by any means, but require a mutation in a specific genetic coding sequence- the cypX or yvmC polynucleotide coding sequence.

Status of Claims:

9. The prior art has taught the complete genome sequence of *Bacillus subtilis*. Further, the prior art teaches hypothetical proteins which are cytochromes and match the protein sequence encoded by SEQ ID NO:1. A hypothetical conserved protein designated yvmC is also deduced from the complete genome sequence and matches SEQ ID NO:8 by 98.8% identity. However, it is not taught that this protein is a red pigment protein.

The prior art does not teach or suggest mutating the cypX gene comprising the nucleotide sequence set forth in SEQ ID NO:1 and/or the yvmC gene comprising the

nucleotide sequence of SEQ ID NO:7, much less mutating them in order to stop red pigment production. Mutant bacterial cells comprising these mutated genes are not taught or suggested by the prior art. The instant claims are free of the prior art, but must overcome the 112, 1st rejections before they are deemed allowable.

10. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser
Primary Examiner
Art Unit 1645

2/9/07